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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/530,702	05/04/2000	TAKASHI GOTO	2000-0578A	3474

7590 07/11/2002

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EXAMINER
TAYLOR, JANELL E

ART UNIT	PAPER NUMBER
1634	10

DATE MAILED: 07/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/530,702	GOTO ET AL.	
	Examiner	Art Unit	
	Janell Cleveland Taylor	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-17* is/are pending in the application.

4a) Of the above claim(s) *18-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

The following is a **FINAL REJECTION**. Any rejection not reiterated is withdrawn. A "Response to Arguments" section follows.

Election/Restrictions

1. Due to Applicant's amendment of June 3, 2002, group II has been rejoined with group I, and all the claims are now examined together. Since all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, the restriction requirement made in Paper No. 4 is hereby withdrawn.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 12-18, 20 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffith et al. (Journal of Biological Chemistry, Vol. 260, No. 4, pp. 2218-2225, 1985, made of record in the IDS submitted 8-30-01).

Griffith et al. teaches "Heparin cofactor II was purified 1800 fold from human plasma to further characterize the structural and functional properties of the protein." (Abstract.) Griffith also teaches that a "partially degraded form of heparin cofactor II was obtained..." (Abstract). Since Griffith teaches that the HCII and the partially degraded HCII were separated, and in fact compared to each other in an assay, the purified HCII must have been free of the degraded HCII, as well as the degrading factor.

Also, since the HCII was purified, it would have also been free of an infective virus as well. Therefore, Griffith anticipates all of the limitations of claims 12-17. Griffith also anticipates all of the limitations of claims 18, 20, 24, 26, and 36, as they teach an isolation procedure for purifying HCII 1800-fold from human plasma, and teach chromatographing the samples (page 2220, and Figure 7).

2. Claims 18, 20, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Tollefsen et al. (Journal of Biological Chemistry, Vol. 257, No. 5, March 10, 1992).

Tollefsen teaches a method for producing a heparin cofactor II-containing preparation substantially free of a degrading factor, comprising separating heparin cofactor II and a degrading factor from a solution containing the heparin cofactor II and the degrading factor, to obtain the heparin cofactor-II containing preparation free of degrading factor. Specifically, in the "Experimental Procedures" section, Tollefson teaches applying the plasma containing HCII to a column of DEAE sepharose, and then washing the column with buffer and eluting it. The pooled protein was then diluted and applied to a column of heparin-sepharose and washed again. The heparin cofactor assay detected HCII and HCII and ATIII were separated by chromatography on heparin-sepharose. (Figure 2). The concentrated protein was chromatographed on a column. The purified HCII was determined to consist of a single polypeptide chain with an apparent 72,000 Mr as determined by SDS-gel electrophoresis. The HCII was obviously purified, then, as the partially degraded heparin was known to have a significant portion (Mr=8000) of the NH2 terminus missing.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 19 and 21-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffith in view of Rosenberg (Journal of Biological Chemistry, Vol. 248, No. 18, 1973).

As disclosed above, Griffith et al. teaches "Heparin cofactor II was purified 1800 fold from human plasma to further characterize the structural and functional properties of the protein." (Abstract.) Griffith also teaches that a "partially degraded form of heparin cofactor II was obtained..." (Abstract). Since Griffith teaches that the HCII and the partially degraded HCII were separated, and in fact compared to each other in an assay, the purified HCII must have been free of the degraded HCII, as well as the degrading factor. Also, since the HCII was purified, it would have also been free of an infective virus as well. Griffith also teach an isolation procedure for purifying HCII 1800-fold from human plasma, and teach chromatographing the samples (page 2220, and Figure 7).

Griffith does not teach that the type of chromatography used is affinity chromatography using a basic amino acid as a ligand. Griffith also does not teach purification by gel filtration, or a step of filtering for virus removal.

Rosenberg teaches the purification and mechanism of action of human antithrombin-heparin cofactor. Specifically, Rosenberg teaches an affinity

chromatography column. Rosenberg teaches "since amino groups are essential in binding heparin to the matrix, purified heparin with covalently attached amino acids and polypeptides were employed [in the chromatographic reaction]." (page 6491, second column.) Rosenberg also teaches using gel filtration as well as "ultrafiltration" to further purify the heparin.

It would have been obvious to one of ordinary skill in the art to modify the teachings of Griffith with those of Rosenberg. This is because using an affinity chromatography column with attached amino acids would have been essential to the capture of heparin, as well as HCII. Furthermore, using basic amino acids would have been obvious as it was well established in the art that basic amino acids would have been useful in capturing certain polypeptides. Furthermore, it would have been obvious to purify the HCII as much as possible, and both gel filtration and ultrafiltration would have helped achieve this goal, which would have resulted in the purest product available.

5. Claims 19 and 21-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tollefsen in view of Rosenberg (Journal of Biological Chemistry, Vol. 248, No. 18, 1973).

As disclosed above, Tollefsen teaches a method for producing a heparin cofactor II-containing preparation substantially free of a degrading factor, comprising separating heparin cofactor II and a degrading factor from a solution containing the heparin cofactor II and the degrading factor, to obtain the heparin cofactor-II containing preparation free of degrading factor. Specifically, in the "Experimental Procedures"

section, Tollefson teaches applying the plasma containing HCII to a column of DEAE sepharose, and then washing the column with buffer and eluting it. The pooled protein was then diluted and applied to a column of heparin-sepharose and washed again. The heparin cofactor assay detected HCII and HCII and ATIII were separated by chromatography on heparin-sepharose. (Figure 2). The concentrated protein was chromatographed on a column. The purified HCII was determined to consist of a single polypeptide chain with an apparent 72,000 Mr as determined by SDS-gel electrophoresis. The HCII was obviously purified, then, as the partially degraded heparin was known to have a significant portion (Mr=8000) of the NH2 terminus missing.

Tollefsen does not teach that the type of chromatography used is affinity chromatography using a basic amino acid as a ligand. Tollefsen also does not teach purification by gel filtration, or a step of filtering for virus removal.

Rosenberg teaches the purification and mechanism of action of human antithrombin-heparin cofactor. Specifically, Rosenberg teaches an affinity chromatography column. Rosenberg teaches "since amino groups are essential in binding heparin to the matrix, purified heparin with covalently attached amino acids and polypeptides were employed [in the chromatographic reaction]." (page 6491, second column.) Rosenberg also teaches using gel filtration as well as "ultrafiltration" to further purify the heparin.

It would have been obvious to one of ordinary skill in the art to modify the teachings of Tollefsen with those of Rosenberg. This is because using an affinity

chromatography column with attached amino acids would have been essential to the capture of heparin, as well as HCII. Furthermore, using basic amino acids would have been obvious as it was well established in the art that basic amino acids would have been useful in capturing certain polypeptides. Furthermore, it would have been obvious to purify the HCII as much as possible, and both gel filtration and ultrafiltration would have helped achieve this goal, which would have resulted in the purest product available.

6. Claims 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffith in view of Rosenberg and further in view of Shimizu et al. (USPN 5,681,463).

As disclosed above, Griffith et al. teaches "Heparin cofactor II was purified 1800 fold from human plasma to further characterize the structural and functional properties of the protein." (Abstract.) Griffith also teaches that a "partially degraded form of heparin cofactor II was obtained..." (Abstract). Since Griffith teaches that the HCII and the partially degraded HCII were separated, and in fact compared to each other in an assay, the purified HCII must have been free of the degraded HCII, as well as the degrading factor. Also, since the HCII was purified, it would have also been free of an infective virus as well. Griffith also teach an isolation procedure for purifying HCII 1800-fold from human plasma, and teach chromatographing the samples (page 2220, and Figure 7).

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Neither Griffith nor Rosenberg teach that the filtration uses a porous hollow fiber.

Shimizu teaches a portable liquid purifying device having activated carbon filter and micro-porous membrane filter, comprised of porous, hollow fibers. (Abstract).

It would have been obvious to use a purifying device which was composed of porous, hollow fibers as this would have allowed for the filtration of the substance over

an expanded area, which would have further purified the substance from its original state.

7. Claims 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tollefsen in view of Rosenberg and further in view of Shimizu et al. (USPN 5,681,463).

As disclosed above, Tollefsen teaches a method for producing a heparin cofactor II-containing preparation substantially free of a degrading factor, comprising separating heparin cofactor II and a degrading factor from a solution containing the heparin cofactor II and the degrading factor, to obtain the heparin cofactor-II containing preparation free of degrading factor. Specifically, in the "Experimental Procedures" section, Tollefson teaches applying the plasma containing HCII to a column of DEAE sepharose, and then washing the column with buffer and eluting it. The pooled protein was then diluted and applied to a column of heparin-sepharose and washed again. The heparin cofactor assay detected HCII and HCII and ATIII were separated by chromatography on heparin-sepharose. (Figure 2). The concentrated protein was chromatographed on a column. The purified HCII was determined to consist of a single polypeptide chain with an apparent 72,000 Mr as determined by SDS-gel electrophoresis. The HCII was obviously purified, then, as the partially degraded heparin was known to have a significant portion (Mr=8000) of the NH2 terminus missing.

Tollefsen does not teach that the type of chromatography used is affinity chromatography using a basic amino acid as a ligand. Tollefsen also does not teach purification by gel filtration, or a step of filtering for virus removal.

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It would have been obvious to one of ordinary skill in the art to modify the teachings of Tollefsen with those of Rosenberg. This is because using an affinity chromatography column with attached amino acids would have been essential to the capture of heparin, as well as HCII. Furthermore, using basic amino acids would have been obvious as it was well established in the art that basic amino acids would have been useful in capturing certain polypeptides. Furthermore, it would have been obvious to purify the HCII as much as possible, and both gel filtration and ultrafiltration would have helped achieve this goal, which would have resulted in the purest product available.

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It would have been obvious to use a purifying device which was composed of porous, hollow fibers as this would have allowed for the filtration of the substance over

an expanded area, which would have further purified the substance from its original state.

Summary

Claims 12-18, 20 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffith et al. Claims 18, 20, and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Tollefsen et al. Claims 19 and 21-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffith in view of Rosenberg. Claims 19 and 21-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tollefsen in view of Rosenberg. Claims 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffith in view of Rosenberg and further in view of Shimizu et al. Claims 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tollefsen in view of Rosenberg and further in view of Shimizu et al.

Response to Arguments

8. Applicant's arguments filed April 23, 2002 have been fully considered but they are not persuasive. First, Applicant argues that the 102(b) rejection of claims 12-17 by Griffith is inappropriate because they do not teach a purified HCII. Applicant argues that because the authors added a high concentration of DFP to the HCII pool, the authors considered that the HCII pool might be contaminated with protease. However, the authors were adding the DFP in an effort to prevent the HCII from degrading, and furthermore, found that adding the DFP, which would have prevented the action of protease from degrading HCII, had no effect upon the degradation of DFP. This means that there was probably no protease present, as the DFP had no effect upon the

degradation rates. Furthermore, the authors had substantially purified the HCII and shown it to be purified using column column chromatography. Secondly, Applicant argues that because the DFP did not inhibit subsequent degradation, that this means that some degrading factor could not be inhibited and remained in the pool. However, this argument is not valid because the authors were doing an analysis over an extended amount of time, and were finding that HCII spontaneously degraded over time. (In the example given, the HCII was stored for a month before it was tested for degraded HCII, at which point they found that 50% had been degraded.) Therefore, the sample started out pure, and over time degraded. There would have been no way for the practitioners to have measured the amount of degradation as a factor of time if the sample had not started out being substantially pure. Thirdly, Applicant argues that the Examiner's statement that the HCII was free of an infective virus was incorrect, because onlyA280 and HCII activity were detected. However, because the sample was purified by chromatography and carefully characterized by molecular weight, the sample would have been purified from any virus during the process of chromatography and gel electrophoresis.

Conclusion

1. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiries of a general nature relating to this application, including information on IDS forms, status requests, sequence listings, etc. should be directed to the Patent Analyst, Chantae Dessau, whose telephone number is (703) 605-1237.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janell Taylor Cleveland, whose telephone number is (703) 305-0273.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (703) 308-1152.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1634 via the PTO Fax Center using (703) 872-9306 or 872-9307 (after final). The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Janell Taylor Cleveland

July 1, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600